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Abstract: Leprosy control has seen little innovation and only limited progress over the last decade. However, research pertaining to the disease has increased as of late, and important innovations are underway. Here, we comment on current efforts to develop tools and approaches to detect leprosy patients and stop the transmission of Mycobacterium leprae, the causative agent of the disease. The tracing and screening of contacts of known leprosy patients promises to strengthen early diagnosis while preventive chemotherapy reduces the risk that contacts develop the disease by 50-60% within two years of administration. Up to now, diagnosis has been mainly based on the presence of signs and symptoms but efforts are underway to develop inexpensive, reliable, point-of-care tests to diagnose infection. Developing a leprosy-specific vaccine that boost long-lasting T-cell responses is also a current research objective. As for launching a programme to interrupt transmission, two interlinked tools, epidemiological modelling and the concept of an investment case, are being developed to explore the feasibility and costs of such a programme, and its overall impact on individuals and society. We conclude that sustained innovation is needed, and that only a combination of tools and approaches holds promise of ending M. leprae transmission.

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Innovative tools and approaches to end the transmission of *Mycobacterium leprae*

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Summary

Leprosy control has seen little innovation and only limited progress over the last decade. However, research pertaining to the disease has increased as of late, and important innovations are underway. Here, we comment on current efforts to develop tools and approaches to detect leprosy patients and stop the transmission of *Mycobacterium leprae*, the causative agent of the disease. The tracing and screening of contacts of known leprosy patients promises to strengthen early diagnosis while preventive chemotherapy reduces the risk that contacts develop the disease by 50-60% within two years of administration. Up to now, diagnosis has been mainly based on the presence of signs and symptoms but efforts are underway to develop inexpensive, reliable, point-of-care tests to diagnose infection. Developing a leprosy-specific vaccine that boost long-lasting T-cell responses is also a current research objective. As for launching a programme to interrupt transmission, two interlinked tools, epidemiological modelling and the concept of an investment case, are being developed to explore the feasibility and costs of such a programme, and its overall impact on individuals and society. We conclude that sustained innovation is needed, and that only a combination of tools and approaches holds promise of ending *M. leprae* transmission.

Introduction

“Leprosy, one of the most ancient, feared and disabling diseases of humankind, is on the verge of defeat”, according to a WHO report published in 2006.¹ Today, the causative agent of the disease, *Mycobacterium leprae*, is still transmitted to humans in at least 122 countries, where over 200 000 new leprosy patients, including around 25 000 children, are being discovered every year.^{2,3} There are several factors responsible for the continuing transmission of the infection.⁴ Delayed diagnosis, which allows transmission to contacts and progression of the disease leading to nerve function impairment, is the most common.⁵ Reasons for delayed diagnosis include disregard of early symptoms, difficulties in the differential diagnosis and fear of stigma from community members. As a result, many people with suspected signs or symptoms of leprosy do not seek health care.⁵ Misdiagnosis by health professionals is another factor that delays diagnosis and perpetuates transmission of the infection.⁵ Compounding these issues is the fact that most leprosy patients live in poor and marginalized communities,⁶ where the experienced staff and facilities required to establish a diagnosis are often lacking. Once diagnosed and classified properly as paucibacillary (PB) or multibacillary (MB) leprosy, patients can be managed efficiently with multi-drug therapy (MDT).⁷

Underlying the difficulties to diagnose leprosy and stop *M. leprae* transmission is our incomplete understanding of the route and mechanism whereby *M. leprae* enters the human body.⁸ Various routes of entry have been proposed, including human-to-human transmission via prolonged direct skin contact or through aerosols, direct inoculation through traumata, and direct or insect-mediated infection from zoonotic or environmental reservoirs.⁴ The most common route of transmission is thought to be direct contact or aerosols in the frame of prolonged exposure to an untreated *M. leprae*-infected subject, especially a MB patient with multiple lesions who is closely related to the contact.⁹ There is also solid evidence that zoonotic *M. leprae* reservoirs exist, most notably the nine-banded armadillo in southern States of the US,^{4,10} but they probably are of negligible relevance for the global epidemiology of the disease.¹¹ Of note, a high proportion of newly detected leprosy patients in endemic areas are unable to identify the source of their infection. This has been explained by the long incubation period of the disease but also indirect transmission, such as from water or soil.¹² Host factors including genetic predisposition and the immune and nutritional status also appear to be important risk factors for leprosy infection.¹³ The lack of basic tools is hampering attempts to gain a better understanding of transmission: there is no way of growing *M. leprae* in culture media, easily handled animal models are unavailable, and the incubation period is long. The role of improved socio-economic conditions is also debated as a negative correlation between leprosy incidence and gross domestic product (GDP) has been observed in several countries.¹⁴⁻¹⁷ However, the causal relationship between the socio-economic development of a country and the risk to an individual of developing leprosy is much less clear.

In 1991, WHO passed a resolution to eliminate leprosy as a public health problem by 2000, defining elimination as a global prevalence of less than one leprosy patient per 10 000 population. Today, of the 122 countries where leprosy is endemic, 120 have reached the WHO elimination goal,¹⁸ not least due to a shortening of the standard treatment duration.¹⁹ A further reduction is currently discussed.²⁰ In 2012, WHO set a goal for “global elimination” of leprosy by 2020 in the frame of its roadmap “accelerating work to overcome the global impact of neglected tropical diseases”.¹⁸ In many countries, however, transmission is still continuing, and the goal appears unattainable.³ In 2016, WHO published the *Global Leprosy Strategy 2016 – 2020* that aims at achieving the more modest

targets of lowering the global prevalence of newly diagnosed people with grade 2 disability (i.e. visible deformity or damage) to below one per million of the population and of zero disabilities among new paediatric patients while maintaining the vision of a leprosy free world.²¹ The strategy is based on reducing stigma in order to achieve early diagnosis, strengthening of referral systems, conducting systematic tracing of household contacts, monitoring of drug resistance, simplifying treatment approaches, and assessing the role of post-exposure prophylaxis.²¹ Although interrupting transmission is part of the vision driving this new strategy, it lacks a strong agenda towards accelerating leprosy diagnosis and prevention.

A better understanding of *M. leprae* transmission and the risk factors for infection as well as improved possibilities to study *M. leprae* are needed to develop more effective tools and interventions to interrupt transmission.²² This article summarizes recent work to develop new strategies and tools the authors consider critical to halt the transmission of *M. leprae*: targeted screening with diagnostic tools to identify leprosy patients. Innovative ways of preventing the disease, such as by administering chemo- or immunoprophylaxis to individuals at risk of infection. And transmission models and investment cases for devising new paths to the interruption of *M. leprae* transmission.

Finding *M. leprae*-infected people, and reducing the risk of contacts

Active case finding involves reaching contacts of index patients and screening them for signs of leprosy. It contributes to achieving early diagnosis and is thus an effective means of reducing the risk of disability in leprosy patients and of curbing transmission of *M. leprae*.²³⁻²⁵ The risk of a contact of an index patient developing leprosy is related, among other factors, to the duration and closeness of the contact, consanguinity with the index patient, and the type of leprosy of the index patient.^{26,27} Screening should be confined to people whose contact with the index patient lasted many hours per week over a period of several months.^{9,27} Contact tracing may be restricted to household members or include neighbours or social contacts of the index patient, depending on the resources available, local epidemiological factors, and the degree of stigma in the community. Contact tracing should be undertaken as soon as possible after confirmation of leprosy in an index patient and after the first month of MDT treatment.²¹ It is ideally carried out by local staff who can readily identify and approach the contacts, examine them and refer those suspected of being infected for confirmatory diagnosis. Alternatively, the contacts of all patients diagnosed over a certain period can be traced in the course of a campaign or special “drive”. This “retrospective active case finding” approach has previously been used in tuberculosis control in Cambodia, where it was found to increase case notification among contacts.²⁸

With regard to post-exposure chemotherapy, several anti-leprosy drugs given in different combinations and regimens have been tested in clinical trials for their ability to reduce the risk of contacts developing the disease.²⁹⁻³¹ The most robust evidence to date confirming the protective potential of post-exposure chemoprophylaxis in contacts of index patients comes from a cluster randomized, double blind and placebo-controlled trial in Bangladesh in which a single dose of rifampicin given to contacts of leprosy patients reduced the incidence of leprosy among the contacts by 57% (95% CI: 33-72%) over the first 2 years of the study.³² The protective effect differed between contact cohorts but persisted throughout the 6-year follow-up of the study.³³ The presumed risk that rifampicin prophylaxis given to leprosy patients might induce or amplify rifampicin resistance to

tuberculosis has been examined and found to be negligible, and therefore outweighed by the protective benefits of the procedure.³⁴

Vaccination with *Bacille Calmette-Guérin* (BCG) at birth or later has also been shown to provide a certain degree of protection from leprosy³⁵ that adds to the protective effect of single-dose rifampicin.⁹ The Bangladesh study showed that single-dose rifampicin given to contacts of leprosy index patients who had received BCG at infancy reduced the risk of leprosy among the contacts by 80% (95% CI: 50–92%).³⁶

Initial evidence of the effectiveness of contact tracing followed by chemoprophylaxis in reducing new case detection rates and grade 2 disability rates^{24,37} prompted the establishment of a Leprosy Post-Exposure Prophylaxis (LPEP) programme designed to study the effectiveness and feasibility of active contact tracing combined with single-dose rifampicin administration in various country settings with differing leprosy programmes.³⁸ The LPEP programme is currently operating in eight countries. Moreover, research groups in Brazil and Bangladesh are assessing the impact of (re-)vaccinating leprosy contacts with BCG in addition to single dose rifampicin administration,^{38,39} and the benefits of a test to detect infected individuals among contacts is also under study. However, case finding, whether active or passive, can only identify a limited proportion of all leprosy patients.⁴⁰ Hence the need for integration of contact tracing and post-exposure prophylaxis interventions into national leprosy programmes capable of implementing these interventions in addition to reliable passive case detection, and robust surveillance systems including accurate recording, timely reporting and regular monitoring.²⁴

Vaccines

Chemoprophylaxis for contacts of leprosy patients is partially successful in preventing leprosy.⁴¹ It lacks, however, the ability to protect contacts on subsequent exposure to the leprosy bacillus. Moreover, only a limited number of anti-leprosy drugs are available and their excessive use could lead to drug resistance.³⁴ By contrast, a specific vaccine to induce a long-lasting immune response would prevent future infections. Vaccines are generally seen as essential tools to eliminate a transmissible disease.⁴² The feasibility of inducing protective immunity with a vaccine is supported by the fact that 90% of people infected by *M. leprae* mount a protective immune response to the bacillus. Several leprosy vaccine projects have recently been completed. Clinical trials have been conducted on *Mycobacterium* now known as *M. indicus pranii* or MIP,⁴³ *M. vaccae*,⁴⁴ *M. habana*,⁴⁵ killed *M. leprae*^{35,46,47} and BCG.^{48,49} Recent systematic reviews and meta-analyses suggest that BCG has a protective efficacy of around 50% against leprosy, with greater protection against MB than PB leprosy.^{50,51} In some countries leprosy patients vaccinated with BCG in childhood have been re-vaccinated with BCG on the strength of evidence from a number of studies that multiple BCG vaccination can enhance protection against *M. leprae*.^{35,46} This strategy, however, has not been effective against tuberculosis⁵²⁻⁵⁴ and WHO guidelines do not support BCG re-vaccination. Some studies, even suggest that BCG vaccination or re-vaccination may accelerate the onset of PB leprosy.^{39,55}

Historically, of all the adjuvants used in approved vaccines most are alum-based, i.e. contain aluminium salts. Such adjuvants have been used safely to boost antibody responses for the past 70 years. However, an effective vaccine against leprosy will be one that induces durable Th1-cell responses directed against *M. leprae* antigens. The recent development of safe and effective

adjuvants capable of inducing the desired responses have made possible a new generation of vaccines against intracellular pathogens.⁵⁶ Innovative Th1 inducing adjuvants are already available for use in tuberculosis vaccines⁵⁷ and a whole new generation of adjuvants capable of enhancing T-cell responses is now in advanced stages of development.⁵⁶ A novel strategy for producing a new generation of leprosy vaccines combines both immunological and molecular techniques.^{58,59} Antigen-specific T cells have been used to screen hundreds of *M. leprae* gene fragments for potential use in a vaccine⁵⁸. Thanks to the sequencing of the whole *M. leprae* genome⁶⁰ it is now possible to rapidly synthesize entire *M. leprae* genes and to produce recombinant proteins. These advances have opened the door to the development of the first defined leprosy vaccine, which will be ready for clinical testing in 2017. In a first step, the vaccine might be administered to contacts of leprosy patients together with preventive chemotherapy in a bid to simultaneously rid them from *M. leprae* infection and protect them from future reinfection.³⁰ Vaccine safety has been studied in the armadillo model; findings indicate that a defined vaccine is safe, and actually delays nerve damage.

Diagnostic tools

Leprosy presents in a range of forms. The bacterial load is low at the tuberculoid end of the spectrum while it is high at the lepromatous end. Available serological tests are sensitive for patients with a relatively high bacterial load (MB patients), but insensitive for PB patients for whom T cell based tests are required to support the diagnosis of leprosy. Historically, the diagnosis of leprosy has relied on clinical evaluation of suspected leprosy lesions and the use of a slit-skin smear test that allows a health professional to determine the bacteriological index, which gives an indication of the bacterial load. Indeed, current WHO guidelines refer to clinical diagnosis and classification as key diagnostic tools.²¹ These methods have shortcomings. Clinical evaluation detects disease rather than subclinical infection, and bacteriological assays cannot reliably distinguish between asymptomatic infections and leprosy disease.⁸ Also, the slit-skin test is invasive, lacks sensitivity for PB leprosy, determining the bacteriological index requires robust training and quality control, and is uncorrelated with disease severity.⁶¹

There is a clear need for inexpensive point-of-care diagnostic tests that are highly specific and sensitive, can detect subclinical infection, and could be used either to confirm diagnosis in people with suspected leprosy lesions or to screen contacts of index patients or other population groups at a high risk for leprosy.^{62,63}

Serological test kits often rely on the measurement of antibodies against phenolic glycolipid (PGL)-I. However, anti-PGL-I antibody levels are often detected at low titers in PB leprosy patients.^{64,65} A currently available enzyme-linked immunosorbent assay (ELISA) based on the leprosy IDRI diagnostic-1 (LID-1) and ND-O antigens combined into the single fusion complex (ND-O–LID) is positive for most MB leprosy patients within 90 minutes.⁶⁶ A recent study in leprosy patients from Colombia and the Philippines suggests that this test could eventually replace the skin-slit procedure to confirm MB leprosy due to its good sensitivity (95.7%) and specificity (93.2%), while still requiring a laboratory to perform the test.^{66,67} Of note, the sensitivity of an antibody-detecting test for PB leprosy is low in endemic regions, and a high rate of false-positive test results has been observed in endemic populations.⁶⁶ Efforts to interrupt *M. leprae* transmission would greatly benefit from a diagnostic tool to detect infection rather than disease. The quantitative polymerase chain reaction (qPCR), for example, is highly specific and sensitive and shows promise for diagnosing infection in MB and PB

patients early enough to ensure the prompt treatment needed to prevent disabilities and to reduce *M. leprae* transmission.⁶⁸ However, no qPCR test for the diagnosis of leprosy has yet been validated and carriers without signs of disease exist in endemic areas. The PCR-based techniques that are used to detect pathogen RNA can also determine the viability and therefore transmissibility of an *M. leprae* bacterium strain and could be used in contact screening and surveillance programmes.⁶⁹ PCR amplification of *M. leprae*-specific DNA can be done on a wide variety of tissue sources, including skin biopsies, oral or nasal swabs, and whole blood. However, optimal results are currently obtained by using skin biopsies rather than readily collected samples. In addition, clinical validation and correlation with serological test results are still to be established. An approved PCR-based test is not yet available.^{68,70}

Another approach being investigated by several research teams is based on the host's polarized T-cell immune response to *M. leprae*. The inflammatory cytokine-mediated T helper Type 1 (Th1) cell response is elicited in response to the leprosy bacterium in PB leprosy. Th1-antigen specific responses from PB patients are detectable through *in vitro* cell stimulation assays using protein and peptide based derivatives. Th1 cell-based surrogate tests may detect asymptomatic *M. leprae* infections. Current research on developing such a test focuses on the detection of interferon gamma, other cytokines and biomarker profiles.⁷¹⁻⁷⁴

There is growing interest among leprosy researchers in using nerve enlargement and inflammation in suspected leprosy patients as a surrogate confirmatory diagnostic biomarker. Recent studies have used bilateral high-resolution sonography and colour Doppler imaging to more objectively measure nerve enlargement and inflammation in the ulnar, median, lateral popliteal, and posterior tibial nerves of leprosy patients. The imaging and sonography procedures showed that nerves of leprosy patients are significantly thicker than those of healthy subjects. The clinical relevance of thickened peripheral nerves in contacts of leprosy patients is unclear. Sonography is not invasive and would be more cost-effective than magnetic resonance imaging, which is currently used to determine nerve thickening in suspected leprosy patients. Exploratory studies on the diagnostic potential of this technique are ongoing,^{75,76} but questions remain how any breakthroughs could be operationalized in endemic settings.

Planning *M. leprae* transmission interruption: modelling and investment case

Epidemiological modelling of *M. leprae* transmission and leprosy is essential in designing, guiding, and evaluating leprosy control policies. The Neglected Tropical Disease (NTD) Modelling Consortium,⁷⁷ brings together an international team of disease modellers with an objective to provide quantitative model analyses to support efforts to achieve, among other goals, the WHO goal for leprosy elimination by 2020.¹⁸ Two leprosy compartmental models and one individual-based transmission model have been described in the literature.⁷⁸ Both compartmental models investigate the course of leprosy in populations and the long-term impact of control strategies.^{17,79-81} The individual-based model (SIMCOLEP) focuses on the impact of case finding among contacts of new leprosy patients.^{82,83} The SIMCOLEP model assesses whether leprosy could be eliminated at national and subnational levels by 2020 in different high-burden countries using WHO's definition of elimination.⁸⁴ Predictions indicated that country-level elimination as defined by WHO could be reached in India, Brazil and Indonesia by 2020 but that leprosy is likely to remain above the elimination threshold in most of the current high-endemic regions or districts within these countries.

An analysis of the case detection rates in India using linear mixed-effects regression also suggests a very slow decline in endemic leprosy, with heterogeneity across states and districts.⁸⁵

In a separate study concerning Pará State, an area of high leprosy incidence in Brazil, modelling analyses using SIMCOLEP suggest that under current control activities the number of new leprosy patients will continue to decrease slowly and that elimination of leprosy as a public health problem could possibly be achieved by 2030 or thereabouts if control programmes continue to implement passive case detection, MDT administration, and contact tracing, at the current levels of intensity. Providing chemoprophylaxis to contacts would further lower the new case detection trend.⁸⁶ This finding has been contested by another group that maintains that the current approach neglects a high proportion of the extant leprosy patients and thus is unlikely to result in any substantial and lasting reduction of disease burden and transmission.^{87,88}

An elaborate analysis of data from Thailand using an advanced back calculation method suggested that the fall in incidence in this country over many years could be attributed to the efforts of the country's control programme.⁸⁹ Models can play an important role in testing various assumptions about the transmission of *M. leprae* as many uncertainties remain with respect to transmission dynamics. More importantly, they can also provide an indication of which interventions will have the greatest impact in halting transmission.

Efforts to eliminate a disease may be costly. The decision to commit to elimination should therefore be based on a robust analysis of the benefits, risks, and costs that accrue from such an undertaking.⁹⁰ To meet this requirement, in recent years a so-called elimination or eradication investment case (EIC) procedure has been developed and applied to several neglected tropical diseases (NTDs), such as onchocerciasis, lymphatic filariasis, and human African trypanosomiasis.⁹¹⁻⁹⁶ The EIC approach is particularly appropriate for diseases such as leprosy that incur a high socio-economic burden and for which multiple interventions exist or are being developed. An EIC for leprosy would help to judge whether sustainably interrupting transmission is feasible, what the most promising interventions for achieving that objective would be, and which long-term consequences the chosen interventions would entail. An EIC should also include an assessment of the changes required to the health system in leprosy-endemic countries, an analysis of the likely impact of zero leprosy transmission on economic productivity at the household and population levels, and on social participation.⁹¹ The economic impact of leprosy elimination may turn out to be substantial at the household but not societal level, given the generally low prevalence and highly focal occurrence of the disease amongst the poorest segments of the population.

A recent systematic review study has explored the possibility of constructing an EIC for leprosy (see Panel 1).⁹⁷

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Panel 1: Key findings of a systematic review on constructing a leprosy elimination investment case

A recent systematic review study⁹⁷ identified a number of factors that should be considered when developing a case for investing in the elimination of leprosy. The findings listed below, adapted from this study, are grouped under eight headings, in accordance with an internationally recognized guide on preparing disease investment cases.⁹⁸

1. Disease burden and elimination

- a. The proportion of newly detected leprosy cases in children under 15 years reflects the degree to which *M. leprae* transmission is occurring.
- b. The proportion of patients with grade-2 disability (visible deformity or damage) reflects the degree to which a health system is achieving early detection and prompt treatment of patients.
- c. Many leprosy cases escape detection by the health system.²

2. Current state of the leprosy programme and recent technical advances

- a. The recently developed PCR test is capable of detecting the leprosy bacillus and its resistance to drugs⁹⁹ but its application is limited.
- b. The *M. leprae*-specific anti-PGL-I antibody test has limited applicability, since it is only reliably positive in MB cases.¹⁰⁰

3. Available and new tools and their scope in interrupting transmission

- a. Tracing contacts of index leprosy patients can detect new leprosy patients more effectively than population-based approaches but faces operational and ethical challenges.⁴⁰
- b. Contact tracing followed by administration of chemoprophylaxis and/or vaccination with BCG is currently the most promising approach to halting *M. leprae* transmission.

4. Future requirements during and after transmission interruption

- a. Linking leprosy elimination efforts with programmes working on other neglected tropical diseases (NTDs) ensures the sustainability, efficacy, and financial resilience needed to reach the leprosy elimination goal.^{2,23}

5. Biological and technical feasibility of transmission interruption

- a. Genome-based technology seems likely to facilitate the development of leprosy vaccines and diagnostic tests.¹⁰¹

6. Socioeconomic burden and public goods obtainable

- a. The Disability-Adjusted Life Year (DALY) is not a reliable indicator of the leprosy disease burden.^{102,103}
- b. Leprosy is one of many NTDs associated with poverty.¹⁰⁴

7. Financing leprosy elimination

- a. Information on the costs of providing leprosy services is limited.

8. Health systems and their capacity

- a. Integrating a leprosy programme into the general health system lowers the level of anti-leprosy stigma in a country.
- b. Community based rehabilitation (CBR) is effective in integrated programmes but applied in few health systems.^{105,106}

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Conclusions

The drive to interrupt *M. leprae* transmission and finally eliminate leprosy is entering a critical stage. The causative bacterium is still circulating freely among many communities, and since the turn of the century, the number of new leprosy patients being detected annually has stagnated. One reason is the dwindling of the political and financial commitment required to stop transmission, a

development that resulted largely from a widespread but mistaken belief that leprosy had been eliminated. Today, the leprosy research community, together with other key players on the leprosy scene, has taken up the challenge to revitalise efforts at halting transmission of *M. leprae*. Research is underway on transmission and on the development of new tools and strategies needed to terminate it. Reaching this goal will not be achieved easily or quickly, and the tools to monitor progress towards zero transmission remain to be developed. Also, leprosy will remain a public health and social problem for decades after the successful interruption of transmission due to the long incubation period, leprosy reactions, and the social and economic consequences of the disease.

Sustainability and perseverance will be critical to its success as is constant innovation. Periodic reviews and adjustments will be needed as new tools and approaches are tested. Of particular relevance to efforts at interrupting *M. leprae* transmission is the need for these tools and strategies to be readily usable within the existing health systems, even in the many countries that no longer have dedicated leprosy control programmes and the fine-tuned technical experience and deep understanding of the local epidemiology that these programmes used to have. The development and deployment of new tools and strategies calls for close collaboration between all actors on the leprosy scene, including the research community, international normative agencies such as WHO, national health authorities, non-governmental organizations, and the agencies and institutions that will catalyse the efforts to bridge the gap between hopes and realities.

Panel 2: Search strategy and selection criteria

References for this review were identified through searches of PubMed for articles published up to August 2016, by use of the terms “leprosy”, “*Mycobacterium leprae*”, “transmission”, “chemoprophylaxis”, “vaccines”, “diagnostics” and “modelling”, either alone or in combination. Relevant articles were also identified through searches in the World Health Organization and Infolink websites as well as authors' personal files. Articles resulting from these searches and relevant references cited in those articles were reviewed. Only articles published in English were included.

Panel 3: Key messages

- Leprosy control has stagnated over recent years but novel tools and approaches to diagnose patients and interrupt *Mycobacterium leprae* transmission are being developed.
 - Contact tracing, screening and treatment with single-dose rifampicin contribute to early diagnosis and prevention of future disease.
 - Leprosy-specific vaccines that induce long-lasting T-cell responses and that could be used in contacts to complement chemotherapy are in advanced development.
 - Molecular biology techniques are being used to develop sensitive and specific tests to detect *M. leprae* infection and diagnose leprosy.
 - Epidemiological modelling and a holistic assessment of the investments needed to interrupt *M. leprae* transmission and resulting benefits can help to guide future efforts to eliminate leprosy.
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Contributors

The concept of the paper was developed by Fareed Mirza and Peter Steinmann. Specific chapters were drafted by Peter Steinmann (Introduction, finding *M. leprae*-infected people, conclusions), Steven G. Reed (vaccines), Fareed Mirza (diagnostic tools), and Deirdre Hollingsworth and Jan Hendrik Richardus (modelling and leprosy elimination investment case). The full draft was developed by Peter Steinmann with assistance from John Maurice. All authors reviewed and approved the final draft.

Conflict of interest/declaration of interests

None of the authors declares any competing interests.

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